* Cardiac muscle cells are branched which is diff than skeletal muscle and cardiac muscle cells aren’t dependent on neuronal activity for contraction
* Cardiac muscle cells are connect end to end by intercalated disks
* Desmosomes are mechanical connectors; if one cell is contracting it will pull the other along w/ it
* Gap junctions are electrical connections—allows AP to move from one cell to the next

**Contractile Apparatus**

* Myosin molecule (thick filament)
  + 2 heavy chains and 4 light chains
  + 2 heads have ATPase activity
  + myosin pulls actin inwards toward its tail
* Actin molecule (thin filament)
  + Double stranded α-helical
  + Actin filament is coiled around by TROPOMYOSIN
    - TROPONIN COMPLEX binds TROPOMYOSIN
  + Normally Tropomyosin blocks binding site on actin for myosin—no contraction
  + When calcium binds to TnC, TnT rotates and moves TnI & Tropomyosin out of the way so myosin can bind to actin
    - So ↓ [Ca]i then myosin binding site on actin is blocked🡪 no contraction
    - CALCIUM IS THE SIGNAL AND REGULATOR OF CONTRACTION
* During contraction I band width is ↓ and H band can disappear
* Z line is point of attachment for actin
* Troponins
  + During MI Tn’s are released into circulation
  + TnC for cardiac and skeletal mm are identical so not a good measure for MI
  + TnI and TnT are diff btwn cardiac and skeletal muscle
    - TnI is the best indicator for MI b/c very specific and sensitive
      * TnI peaks w/in first 6 hrs

**Contraction Cycle**

* Goes UNINHIBITED TILL ALL THE ATP IS CONSUMED, WERE IT NOT FOR CACLCIUM SEQUESTRATION
* Biochemical process of contraction depends on ATP
  + Binding of ATP dissociates myosin from actin🡪 myosin head is free and it is an ATPase🡪 rapidly cleaves the ATP🡪 ADP & Phosphate but phosphate isn’t released (the energy released from cleaving Phosphate from ATP is transferred to myosin head)
  + ADP+ P on myosin makes myosin head extend and bind actin
  + After myosin binds actin phosphate is released myosin head flexes🡪 power stroke occurs!
  + ADP is released and myosin dissociates from actin

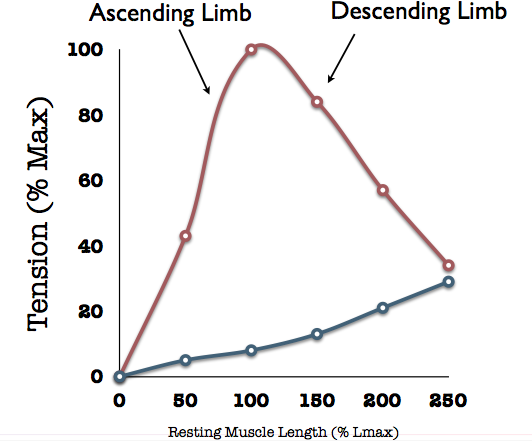
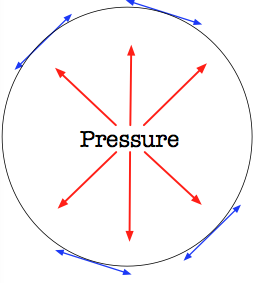
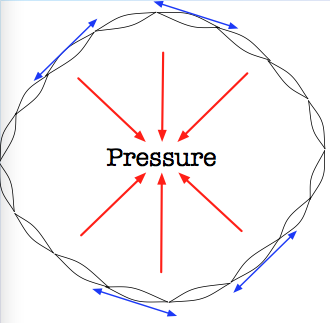
**Calcium Homeostasis in Cardiac Myocytes**

* L-type Ca Channels open during phase 2 of AP and bring in extracellular Ca (essential but not sufficient for cardiac contraction)🡪 this Ca binds TnC and Ryanodine receptors (opens them)🡪 releases stored Ca from w/in SR🡪 this calcium initiates contraction
  + Calcium induced calcium receptors (CICR/ Ryanodine Receptors) on the sarcoplasmic reticulum
* NCX
* SERCA
  + Pumps Ca back into SR during diastole
  + Cardiac contraction ends when Ca is sequestered🡪 induces cardiac diastole
  + Majority of Ca comes from SR and most of it goes back into SR
  + Phospholambam
    - Binds to SERCA and inactivates it causing ↓ Ca sequestration🡪 cardiac muscle cant contract
* Ca-ATPase (minor importance)

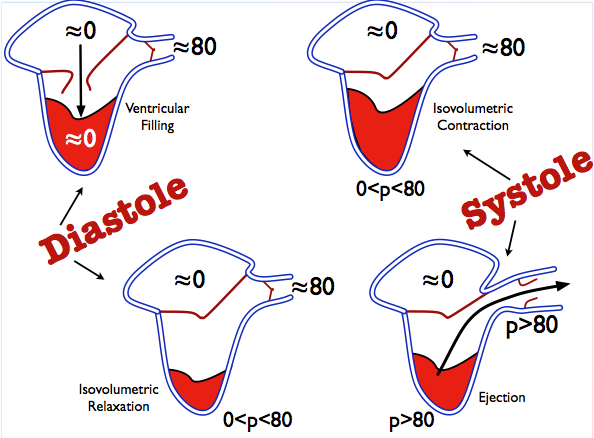
**SNS stimulation affecting Cardiac Contraction**

* SNS activation activates β1 Receptors on the PM (β1 agonists—NE or EPI)
* β1 Receptors are Gs🡪 ↑ cAMP 🡪 ↑ in intracellular Ca 🡪 ↑ contractility
* also activates PKA
* PKA effects
  + Phosphorylation of:
    - Phospholamban
      * causes it to dissociate from SERCA🡪 ↑ SERCA activity 🡪 potentiates relation by removing Ca faster
      * allows a faster relaxation b/c enhances Ca uptake by SR
    - Ryanodine Receptors
      * Potentiates contraction by making more Ca available
    - L-type Ca channels
    - TnC
* \*\*Ultimately the SNS makes the heart work better in systole and diastole
* PSNS has zero effect on cardiac contraction or relaxation b/c no supply below AV node (no innervation to ventricles)

**Cardiac Mechanics**

* Properties of Cardiac Muscle
  + When muscle is pulled w/ preload the elastic recoil of the muscle pulls back and generates passive tension
  + When the muscle gets stimulated it generates active tension
  + ↑ stretch (↑ preload= ↑ passive tension)= ↑ active tension
  + 
    - blue= preload
    - at very high prestretch lengths--no overlap of actin and myosin so too far from eachother to interact
    - Very Low resting length double overlap of actin and myosin causes buckling--cant contract b/c its overcrowded
* At the ascending limb
  + Optimal overlap of actin-myosin
  + Enhanced sensitivity of the contractile proteins (TnC) to Ca
  + Opening stretch activated Ca Channels ↑ Ca entry into the cells
  + HEART ALWAYS OPERATES ON THE ASCENDING LIMB OF THE LENGTH CURVE
    - Only time it will be on descending curve is if pt is experiencing flash pulmonary edema
      * End Diastolic Volume (EDV) ↑ over 120
* In the heart venous return (VR) is stretching the muscle
  + ↑ VR🡪 ↑ stretch 🡪 ↑ performance 🡪 ↑ CO (cardiac output)
* Tension = Pressure X Resistance
  + Tension on the walls of a cavity
    - 
      * every point on the wall of a pressurized cavity faces a force along its circumference
      * this force is tension= wall tension
      * Pressure in arteries is generated by the heart
  + Tension in heart
    - 
      * ventricular myocytes contract along their axis generating tension
      * The perpendicular force vector of all myocytes combined tension is pressure
      * Cardiac myocytes are generating tension and the force in the cavity is pressure
    - CHF—as heart dilates the cardiac myocytes must do more work to generate enough tension to keep the same pressure. This alteration adversely affects coronary supply and ↑ cardiac work. But the reason to heart dilated in the first place was because myocytes weren’t working properly

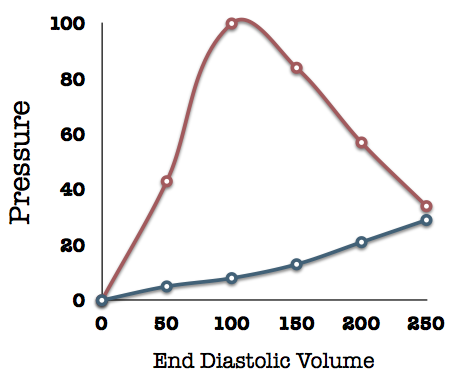
**The Cardiac Cycle**

* 
* Pressure in ventricles is ~0 and Pressure in LA is a little higher so blood goes from area of ↑ P to lower P through mitral valve; this is called VENTRICULAR FILLING (during diastole)
  + As you ↑ ventricular filling you ↑ performance b/c ↑ stretch/preload
* When pressure in LV is more than LA but less than aortic pressure (80) then both the mitral valve and the aortic valve are closed and SA node depolarizes causing AP and contraction🡪the heart is in a state of ISOVOLUMETRIC CONTRACTION
  + Most energy is consumed in this step but no work is done b/c W= FxD
  + This is during systole
* Once the pressure in the LV >80 the aortic valve opens and aorta and LV are one compartment; Blood flows from LV🡪 aorta b/c of pressure difference and this phase of the cycle is EJECTION
  + Once AV opens there is a transient ↑ in aortic pressure do to turbulence
  + Most work is done in this phase
  + Once blood moves downstream in aorta the pressure starts to fall slowly
  + This is also during systole
* When pressure in LV falls below 80 the aortic valve closes (so again aortic and mitral valves are closed) and the LV relaxes—ISOVOLUMETRIC RELAXATION
  + This is during diastole
* Venous Pressure waves
  + A, C, & V waves are venous pressure waves seen in the jugular vein—reflective of ↑ CVP during cardiac cycle
  + A wave
    - Atrial contraction pushing blood into ventricles and also back into veins (no valve between atria and vena cava 🡪 ↑ central venous pressure
  + C wave
    - Seen during isovolumetric contration of the ventricles
    - Pressure in the ventricles ↑ which causes the mitral valve to balloon into the atria🡪 ↑ P in atria🡪 ↑ back pressure in veins
  + V wave
    - End of isovolumetric relaxation b/c when mitral valve opens—atria accumulates blood and the atria passive pressure is the higher

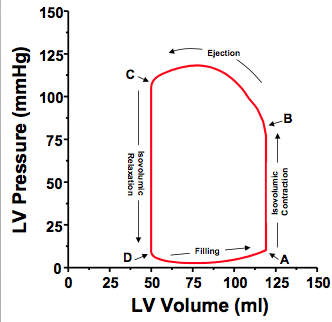
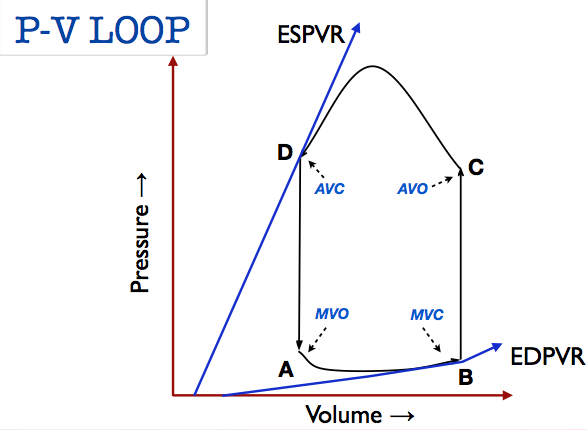
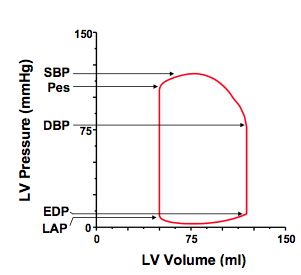
**Cardiac Cycle info from BRS Review**

* Atrial Systole
  + Preceded by P wave (electrical activatin of the atria)
* Isovolumetric contraction
  + Begins after onset of QRS wave (electrical activation of ventricles)
  + Hear 1st heart sound
* Ejection
  + Onset of the T wave which represents repol of the ventricles marks the end of both ventricular contraction and ejection
* Isovolumetric relaxation
  + End of T wave (repolarization of the ventricles is now complete)
  + Hear 2nd heart sounds
* Ventricular Filling
  + Hear 3rd heart sound (flow of blood from A🡪V )

**FRANK STARLING RELATIONSHIP**

* 
  + ↑ stretch (preload)= EDV🡪↑ affinitiy of TnC for Ca🡪↑ force of contraction 🡪 ↑ CO
  + ↑ VR🡪↑ EDV 🡪 ↑ SV 🡪 ↑ CO
  + Preload for RV is estimated as central venous pressure (CVP) or RAP
  + Preload for LV is estimated as LAP by measuring PCWP (Pulmonary capillary wedge pressure)
* INDICES OF CARDIAC PRELOAD
  + LVEDV\*\*\*
  + LVEDP
  + LAP
  + PVP
  + PCWP (most common estimation)
    - This estimated LAP which is proportional to LVEDP
* Preload is a determinant of ventricular performance (the capacity of the ventricle to generate pressure)
  + Intrinsic to the heart (INDEP OF INNERV)
  + Ppl w/ cardiac transplant (deinnervated)—exercise ↑ vasodilation🡪 ↑ flow to skeletal mm🡪 ↑ VR🡪 ↑ preload/EDV🡪 ↑ SV🡪 ↑ CO
    - So these patients can’t ↑ CO through ↑ HR but doesn’t matter b/c can still ↑ CO through Frank-sterling
* Any maneuver that causes the change in SV in one ventricle will rapidly result in a parallel change in SV in the other ventricle

**PRESSURE VOLUME LOOPS**

* 
* 
  + D= ESV
  + B= EDV
* 
  + SBP= systolic BP
  + Pes= pressure at end of systole (always >DBP)
  + DBP= diastolic BP
    - AVO
  + EDP= end diastolic P
  + LAP= left atrial pressure
* These are snap shots in time looking at the ventricles
  + AVO= aortic valve opens
  + AVC= aortic valve closes
  + MVO= mitral valve opens
  + MVC= mitral valve closes
* The P-V loop is constrained by the end systolic pressure volume relationship (ESPVR) and the end diastolic pressure volume relationship (EDPVR)
* Changes in the PV loop
  + ↑ preload/EDV due to ↑ VR🡪 ↑ SV
    - The width of the P-V loop is dependent on stroke volume or venous return
    - So ↑ SV🡪 ↑ width of PV loop
  + ↑ afterload (pressure against which the ventricles are pumping)
    - ↑ in aortic pressure would ↑ afterload
    - If you ↑ the pressure against which the LV is pumping then you ↓ SV which causes the loop to be more narrow
      * C would be higher b/c now need ↑ Pressure for AVO
    - ↓ SV also ↑ ESV so in the above loop D would be shifted R ( and up b/c of the ↑ pressure of aorta will have a higher pressure that the AVC)
  + ↑ contractility
    - the ventricle develops greater tension than usual during systole causing an ↑ in SV this will cause a ↓ in ESV (D shifted to the L)

**Factors Affecting Contractility**

* If you ↑ EDV higher ventricular pressure were observed but the same EDP fell on a near straight line and all EDV were also on near linear slope
  + The ESPVR is reflective of cardiac contractility (ionotropy) and EDPVR of cardiac compliance (lusitropy)
    - Changing contractility
      * ↑ SNS causes ↑ contractility🡪 ↑ SV 🡪 ↓ ESV
      * Calcium channel blockers ↓ contractility 🡪 ↓ SV 🡪 ↑ ESV
* Positive ionotropic state (↑ contractility)
  + Will have same EDV and same DBP/AVO b/c MAP is unchanged during this beat (remember this is snap shot in time during one cardiac cycle)
  + In the next beat you will see a change in MAP b/c ↑ SV from ↑ contractility will cause ↑ in CO
* Contractility is a determinant of ventricular performance (the capacity of the ventricle to generate pressure)
  + This is linked to availability of calcium (↑ intracellular calcium) and the sensitivity of the contractile apparatus to calcium
* What is ↑ contractility?
  + ↑ rate of contraction
  + ↑ peak ventricular pressure
  + ↑ rate of relaxation
    - b/c of activity of SERCA (under influence SNS)
  + ↓ in systolic interval due to faster relaxation
    - also ↓ in diastolic interval b/c ↑ in HR
  + \*\*\*EXCITATION OF THE HEART (AP’s) and CONTRACTION ARE 2 SEPARATE EVENTS LINKED BY CALCIUM
    - so systole is a passive process
    - diastole is an active process
* How do you measure ↑ contractility?
  + Rate of change of ventricular P during ejection at a given EDV (preload)
  + Change in Ejection Fraction = SV/EDVV
    - Normal ~70%
* Functional mechanisms Regulating Contractility
  + ↑ Ca influx across PM
    - ↑ activation of L-Type channels
      * β adrenergic mediated phosphorylation--↑ Ca comes in during plateau phase (2)
    - Positive staircase phenomenon
      * ↑ HR 🡪 ↑ intracellular Ca stores b/c less time to push it out through NCX so it stores it
    - Plasma hypercalcemia and/or hyponatremia reverses NCX and increases intracellular calcium –> ↑ contraction
    - Inhibition of Na/K ATPase (digoxin does this) reverses NCX and increases intracellular Calcium
  + ↑ Ca flux across SR
    - β adrenergic mediated phosphorylation of phospholambam ↑ SERCA uptake of Ca
      * ↑ relaxation
      * This ↑ Ca available for the next cycle (positive ionotropic)
      * Hypoxia w/ ↓ in ATP levels attenuates SERCA 🡪 ↓ Ca stored (negative ionotropic)
  + Systmeic acidosis
    - ↓ the sensitivity of actin-myosin complex to Ca
    - ↓ ionic Ca flux by inhibiting almost all Ca pumps and channels (L-type) (negative ionotropic)
  + Where ↑ systolic Ca enhances contractility, ↑ Ca during diastole impedes relaxation and is met with a stiffer less compliant ventricle

**Factors Affecting SV**

* ↑ contractility 🡪 ↑ ejection🡪 ↑ SV for any given preload
* ↑ preload🡪 ↑ stretch 🡪 enhancing ventricular contraction 🡪 ↑ SV
* ↑ afterload 🡪 ↑ isovolumetric contraction time (b/c needs to reach higher pressure) 🡪 ↓ SV 🡪 ↑ ESV 🡪 next beat will have ↑ VR🡪 ↑ EDV 🡪 ↑ SV
  + Afterload is a function of
    - TPR
    - Aortic compliance
      * ↓ compliance 🡪 ↑ afterload
    - Resistance at the level of aortic valve
      * Stenosed AV 🡪 ↑ in afterload even if MAP is normal

**Systolic Dysfunction**

* manifestation of impaired contractility
  + MI
  + Dilated cardiomyopathy
  + Myocarditis
* ↓ contractility🡪 ↓ ejection 🡪 ↑ in ESV 🡪 ↓ SV and ↓ peak arterial pressure
* ↓ contractility🡪 ↓ slope of ESPVR
* Compensation for systolic dysfunction
  + ↓ SV (LV) 🡪 so you have more blood left in your ventricles which would ↑ pressure in things upstream so ↑ in LAP, pulmonary pressure and RAP 🡪 ↑ in preload 🡪 ↑ EDVV 🡪 ↑ SV
  + initial ↓ in SV results in blood backing up on venous side of circulation which results in next beat having ↑ venous pressure 🡪 ↑ preload 🡪 ↑ SV

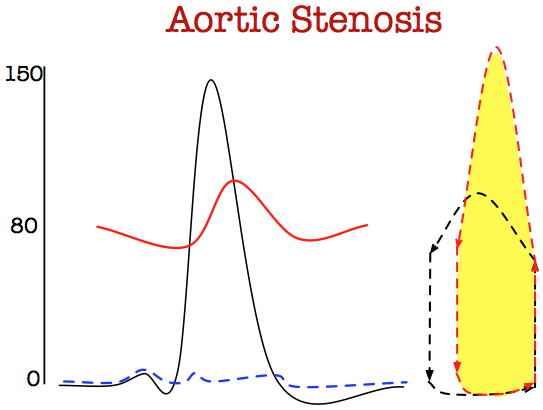
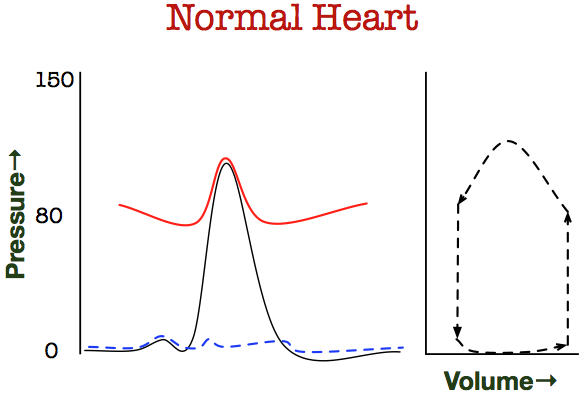
**Diastolic Dysfunction**

* A manifestation of reduced lusitropy (↓ ventricular compliance)
  + MI
  + Hypertrophic cardiomyopathy
  + HTN
  + Cardiac remodeling
  + Amyloidosis
  + Pericardial fibrosis
  + ↓ ventricular compliance 🡪 ↑ ventricular pressure at rest 🡪 ↓ filling 🡪 ↓ EDV 🡪 ↓ SV 🡪 ↓ CO

**Cardiac Work**

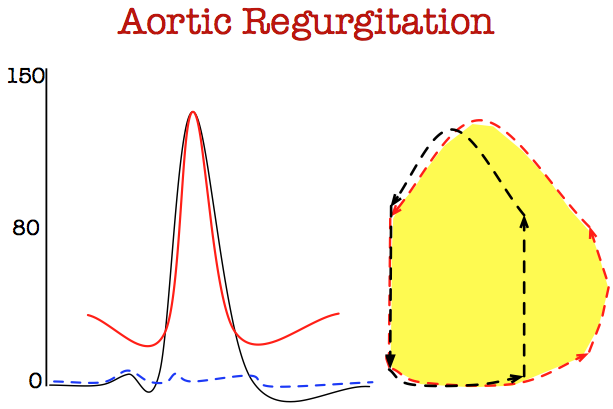
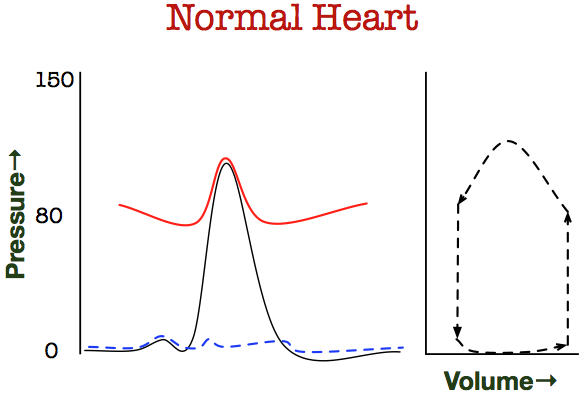
* External work (work to move blood)= P \* V = P \* SV = P (EDV-ESV)
  + Normal is <5%
* Kinetic work= 1/2mv2
  + Normal <1%
* Tension work = T \* change in time
  + Tension against which the mycocardium is pumping (afterload)
  + you need the cardiac tension x the time of contraction (systole).
    - if you ↑ HR🡪 ↑ systole 🡪 ↑ in tension work
* Minute work = HR + [(P \* SV) + (1/2mv2) + (T)]
  + But can ignore kinetic work b/c so small so…
  + = HR + [(P \* SV) + (P \* r)]
    - T= P \* r
      * The LaPlace relationship says that wall tension (T) is proportional to the product of intraventricular pressure (P) and ventricular radius (r)
      * For an individual patient r can be assumed to be constant over time so…
      * Minute work = HR \* P \* SV
* Double product is used for clinical assessment = HR \* P
  + ↓ in either of these will lead to ↓ in tension
  + SV takes time and effort to determine so just use HR and P
  + Can be misleading b/c in aortic stenosis MAP can be normal and this eqn would indicate no ↑ work when in reality it would be so the true reflection of Work = HR \* peak LVP
    - also misleading in systolic HTN (188/47) b/c MAP is still ~100 but b/c of the ↑ in systolic BP🡪 ↑ in Work

**Aortic Stenosis**

****

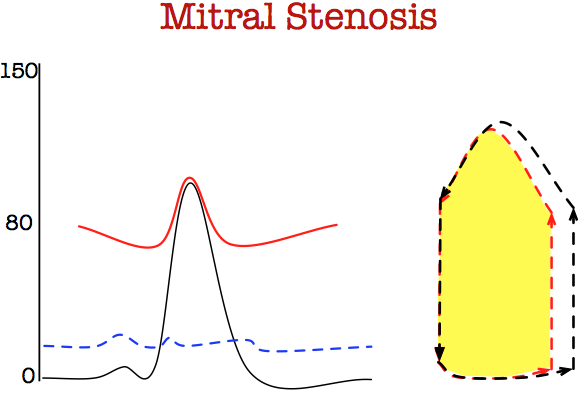
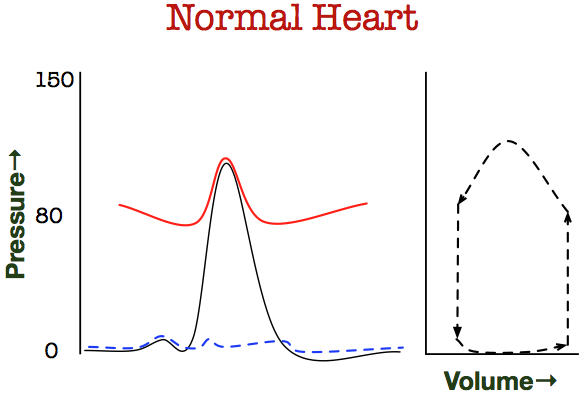
* **Blue= Venous Pressure; Red= aortic pressure; black= Ventricular P**
* In aortic stenosis the radius reduces from 2.5cm2 to less than .5cm2
* Aortic pressure isn’t coupled with LV pressure anymore and the ejection of blood from the ventricles into the aorta is made much harder.
  + Aortic valve becomes a huge site of resistance so it's difficult to pump blood into the aorta. Therefore the ventricular pressure ↑
  + The afterload in this situation becomes much higher than before .
    - Afterload is actually dependent on peak LV pressure
    - aortic pressure is nearly always = afterload. This is the one situation where it is different!!
* AVO is still the same in PV loop
* the peak LV pressure is higher (black line) than normal so ↓ in SV
* aortic pressure is ~ normal b/c it is governed by TPR
* With aortic stenosis the person has exertional dyspnea.
  + when the person starts to exercise, failure of CO to keep up causes them to get fatigued.
* How do you tell it apart from angina:
  + ANGINA DOES NOT PRESENT w/a systolic MURMUR & this does!!!

**Aortic Regurgitation =** Aortic insufficiency



* Distinguishing feature is a widening pulse pressure!
  + Widening of pulse pressure (Systolic-diastolic) b/c systolic ↑ and diastolic ↓
  + The diastolic ↓ because it flew back into the ventricle.
  + Diastolic pressure is a function of aortic recoil with a given volume so b/c normally AV is closed during diastole and in regurg it doesn't close properly🡪less pressure in aorta due to backflow 🡪 ↓ in recoil 🡪 ↓ in diastolic P
* Will hear a murmur during diastole
* Dilation of PV loop
* The aortic valve doesn't close properly during diastole so you get a regurgitation of blood
* Aortic valve doesn't close properly so there is a backflow of blood into the ventricles from the aorta🡪 ↑ EDV 🡪 ↑ SV 🡪 CO 🡪 ↑ MAP

**Mitral Stenosis**

****

* Very similar pressure profiles as compared to a normal person
* The mitral valve is stenosed so the L atria has a hard time pumping blood into L ventricle 🡪 so you would predict that EDV ↓ 🡪 ↓ SV.. but you really just see similar pressure profiles just see changes in the venous pressure profile
* ↑ in venous pressure b/c atrial pressure is ↑ so will see distended jugular veins.